Off-Label Use and the Spectre of Drug-Eluting Stent Thrombosis

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Off-label use of drug-eluting stents (DES) occurs when the implantation takes place outside the scope of the approved label. In the case of DES, the “on-label” indications are limited to short de novo lesions in coronary arteries measuring 2.5 to 3.75 mm in diameter. As anticipated, the use of paclitaxel-eluting stents (PES) has shown excellent outcomes with low rates of target lesion revascularization at long-term follow-up in on-label indications.1

However, generalization of these data to the general population is problematic, because most patients fall into the “off-label” indication, which is associated with higher periprocedural risk. Since its launch in March 2004, thanks to its demonstrated ability to decrease target lesion revascularization, indications for PES were rapidly extended to those who would benefit most from it, such as patients with diabetes, renal failure, very small vessels, very long lesions, chronic total occlusions, bifurcations, left main coronary artery disease, in-stent restenosis, multivessel disease, acute myocardial infarction, or saphenous vein graft disease. In general, the more complex the case is, the more likely the occurrence of adverse events. Accordingly, the US Food and Drug Administration (FDA) required manufacturers to follow-up patients in the original clinical trials for 5 years after implantation and conduct registry studies of consecutively enrolled new patients, to collect data on “real-world” use.2

The emergence of the adverse events logically materialized with an increased incidence of very late stent thrombosis (ST). Concerns arose about the impact of this rare complication on cardiac mortality, and the concerns of the scientific community reached their peak at the end of 2006. The article by Lasala et al3 in this issue of Circulation: Cardiovascular Interventions was born out of this surveillance program. The first Peri-Approval Registry: A Multi-Center Safety Surveillance (ARRIVE) trial was an FDA-mandated postmarketing trial that enlisted 2588 all-comer patients having 3768 lesions and 4206 stents between February and May 2004. In October 2004, it was expanded by the ARRIVE II registry, which was industry initiated and enrolled 5007 all-comer patients with 7014 lesions and 7772 stents. With 103 large-volume US centers taking part in the registries and 65% of PES implantations being off label, the 2 registries became an inestimable help for evaluating the global safety profile of PES. This help was welcomed in December 2006, when the FDA convened an extraordinary session to consider global safety of DES.

At that point of time, the crux was the evaluation of the global safety profile of DES in comparison with bare metal stent in on- and off-label indications. Highlighted as a warning label in the New England Journal of Medicine,2 the FDA concluded that “as compared with on-label use, off-label use is associated with increased risks of stent thrombosis and death or myocardial infarction.”

What to Derive From ARRIVE?

What can one learn from these registries that were designed to reflect in aggregate the current practice in the United States (103 centers nationwide) and that allow generalization to all comers?

- First, 65% of patients included in the registries had an off-label indication. This closely matches with other “all-comer” trials. In the DES cover Registry, 2588 (47%) of the 5541 patients received DES for an off-label or untested indication.4

In the EVENT trial, 1817 (56%) patients of 3323 underwent off-label DES implantation.5 In the analysis done by the Wake Forrest University, off-label indications were found in 854 of 1135 patients treated with bare-metal stent (75%) and in 993 of 1242 patients with DES (80%).6 In the National Heart, Lung, and Blood Institute Dynamic Registry analysis, Marroquin et al7 demonstrated that 2110 of 3858 patients who received a bare-metal stent (55%) and 1312 of 2693 patients who received a DES (49%) were treated in an off-label fashion. In the LEADERS trial, 696 of 857 patients who received a biolimus-eluting stent (81%) and 665 of 850 patients who received a sirolimus-eluting stent (78%) received treatment for off-label indications.8

- Second, the 24-month cumulative incidence of Academic Research Consortium (ARC)-definitive ST was 2.6%. This is clearly higher than the rate of ST in stable patients undergoing percutaneous coronary intervention in elective conditions (0% to 1.5%). However, the incidence stays within the range (1.5% to 3.3%) found in other “all-comer” trials9–11 and corresponds well to the 2.5% cumulative incidence found in the 3891 patients with PES in the Bern-Rotterdam cohort.10

- Third, the main risk factors for ST are off-label indications per se, such as presence of moderate-to-severe calcifications, small reference vessel, long stent segments, previous

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brachytherapy, renal failure, or premature discontinuation of thienopyridine. A more detailed multivariate time series analysis showed early (<1 month after implantation) ST represents 42% of all ST and is associated with inflow and outflow problems, such as suboptimal end result (dissection, thrombus, severe calcification, multiple stents, long-stented segments) and procoagulable states (cessation of thienopyridines and congestive heart failure). Late ST (between 1 month and 1 year) composed 28% of all ST and is associated with more extended coronary disease (small vessel, diabetes, smoking, and multivessel disease) and cessation of thienopyridines. Very late ST made up 30% of all ST and is associated with biological factors impairing endothelialization and coronary remodeling, such as previous brachytherapy, vein graft disease, or renal failure. Finally, an initial ST is a risk factor for a second event (ST risk after initial ST: 4% per year).

Where Are We Now?

Taken together, these findings support our current interpretation of ST. The Figure represents the schematic illustration of the histopathologic findings in patients suffering from ST. WBC/HPF indicates average number of white blood cells per high-power field. Adapted from Refs. 17 and 19, with permission.

The early period after stent implantation is prothrombotic per se because of the accumulation of risk factors inherent to the procedure, such as the complete absence of endothelialization of the stent struts and the presence of local inflammation triggered by the angioplasty. Therefore, any additional triggers—such as a slow flow due to inflow and outflow problems (thrombus, dissection, hematoma, and distal embolization), decreased left ventricular function, procoagulable state, or incomplete inhibition of platelet activation—will allow the thrombus to build. Early ST is consistently associated with clinical setting and operator factors, such as poor postprocedural result, acute coronary syndromes (patients with acute myocardial infarction in ARRIVE have a 1.6% incidence of early ST), and inadequate inhibition of platelet aggregation. As polymers have antithrombotic properties and drugs eluted by DESs have anti-inflammatory effects, DESs should have a lower incidence of early ST. It is possible that because the interventionist usually prefers to stent longer with DESs than with bare-metal stents, this hypothetical beneficial effect was not translated into clinical benefits in all-comer trials.

Late ST occurs in patients having less important (or continual) prothrombotic factors than patients described earlier. It is therefore associated with biological patient-related factors and insufficient inhibition of platelet aggregation. As an example, according to the metabolic state of patients with diabetes mellitus or renal failure, the prothrombotic factors may become sufficient to progress to ST in incompletely expanded coronary stent.

Taken together, the evidence accumulated so far on early and late ST should strengthen our resolve to strive for optimal
postprocedural result, careful patient selection, and timely and appropriate inhibition of platelet aggregation. Special emphasis should be put on patient selection and dual antiplatelet therapy, as this trial confirms previous reports.12–15 In this study, premature discontinuation is associated with a 14-fold increase in early and 2-fold late ST.

Very late ST, however, is a distinct entity complicating the use of first generation DES. Bare-metal stent studies such as that from Yokoyama et al16 suggest that very late ST may be secondary to the neointimal remodeling and dissection. However, in DES, autopsy and ultrasound studies of patients with very late ST suggest that very late ST is caused by an extensive vasculitis of the stented segment. Different inflammatory patterns were reported, suggesting different types of delayed hypersensitivity reactions with secondary upset of normal re-endothelialization, exaggerated vessel remodeling, and generation of a prothrombotic medium.17–19 To date, the most relevant risk factors for very late ST are acute coronary syndrome at time of the index procedure, long stent segment, and possibly atopy.

As compared with on-label use, off-label use is associated with an increased risk of ST. This was anticipated because the principal risk factors for ST are exclusion criteria of the FDA-approved randomized controlled trials. Nevertheless and as recently demonstrated in the meta-analysis by Kirtane et al,20 the use of DES in on- and off-label indications seem to be safe.

Conclusions

The ARRIVE registries arose from an FDA surveillance program and fulfilled their mission during the turbulent period of the so-called “2006 European Society of Cardiology (ESC) firestorm.” The evidence accumulated to date—mainly derived from the concern of the scientific community engendered by this firestorm—demonstrates an acceptable DES safety profile in on-label and off-label indications. Moreover, this research effort gives us a better comprehension of ST and updates the concept of vascular remodeling. A coronary artery is not only a very dynamic medium that is, on one hand, at risk of chronic and devastating inflammation but also, on the other hand, is able to heal. New stent technologies like bioabsorbable stents may help further to define percutaneous coronary intervention-associated vascular remodeling and hopefully permit a significant reduction in the occurrence of ST. We now enter a new era, guided by an old concept: the one of plaque sealing!

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Disclosures

None.

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